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Incidence of malignant hyperthermia reactions in 2,214 patients undergoing muscle biopsy

To determine the incidence of malignant hyperthermia (MH) reactions after trigger-free anaesthesia in a large population of MH-susceptible (MHS) patients, the charts of 2,214 patients who underwent elective muscle biopsy for malignant hyperthermia were reviewed. Either general or regional anaesthesia with non-triggering drugs was used. For general anaesthesia, the trachea was intubated in the absence of muscle relaxants. The halothane/cafeine contracture test was performed on the biopsied muscle. Suspected MH reactions were identified according to their site of occurrence (in the operating room, recovery room or ward). Ninety-seven percent of patients received a general anaesthetic; 3% received a regional anaesthetic or field block. Of the 2214 patients whose muscles were biopsied, 1082 patients were biopsy-positive for MH. Five patients in whom MH reactions were diagnosed in the recovery room were all subsequently proved to be biopsy-positive for MH. Four of the five received intravenous dantrolene as part of their therapy; the fifth received only symptomatic therapy as parenteral dantrolene was not commercially available. All patients recovered completely from their reactions. We conclude that the incidence of MH reactions in biopsy-positive patients who receive a trigger-free anaesthetic for minor surgery is small (0.46%, (0.15–1.07%, 95% CI)). These reactions occur in the immediate postoperative period.

Key words

ANAESTHESIA: general, regional;
COMPLICATIONS: myopathy;
HYPERTHERMIA: malignant.

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Presented in part at the annual meeting of the International Anesthesia Research Society, Orlando, Florida, March 1987.

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Accepted for publication 9th December, 1994.

Dans le but de déterminer l'incidence des réactions d'hyperthermie maligne (HM) après une anesthésie libre d'agent déclenchant dans une population importante de patients susceptibles, les dossiers de 2 214 patients soumis à une biopsie musculaire en chirurgie réglée ont été révisés. Une anesthésie générale ou régionale avait été administrée. Pour la générale, la trachée avait été intubée sans myorelaxants. Le test de contracture à l'halothane/caféine était réalisé sur l'échantillon de muscle prélevé. Les réactions suspectes d'HM étaient identifiées selon l'endroit de leur apparition (salle d'opération, salle de réveil ou étage). Quatre-vingt-dix-sept pour cent des biopsies ont été effectuées sous anesthésie générale et 3% sous régionale ou infiltration locale. Des 2214 patients biopsiés, 1082 étaient positifs pour l'HM. Chez les cinq patients dont le diagnostic avait été fait en salle de réveil, tous avaient une biopsie positive. Quatre de ceux-ci ont été traités au dantrolène intraveineux; comme le dantrolène n'était pas encore sur le marché pour le cinquième, un traitement purement symptomatique a été administré. La récupération a été totale pour tous les patients. Nous concluons que l'incidence des réactions d'HM chez les porteurs d'une biopsie positive est minime lorsqu'ils subissent une biopsie musculaire avec des anesthésiques libres d'agent déclenchant (0,46%, (0,15–1,07%, IC 95%)). Ces réactions surviennent à la période postopératoire immédiate.

During the past 30 years, the mortality from malignant hyperthermia (MH) has decreased from more than 80% to less than 10%. This decrease has been attributed to several factors, including the widespread availability of intravenous dantrolene¹ and an increased awareness and understanding of malignant hyperthermia by physicians.² In the mid-1970s, the only definitive and reliable treatment for MH reactions, a parenteral formulation of dantrolene sodium, became available. The widespread availability of iv dantrolene sodium,³ recognized as one of the most important advances in the management of MH reactions, has decreased both the severity of and the mortality from acute MH reactions.⁴ Recognition of the signs and symptoms of MH reactions has also led to early institution of treatment. This has further decreased the mortality from MH by arresting the reaction before ir-

TABLE I Demographic data

Biopsy results	MH ⁺	K-MH	MH ⁻	Total
Number of patients	808	274	1132	2214
Age (yr)*	32.5 ± 14.3	31.4 ± 13.2	32.5 ± 16.1	
Anaesthetic technique				
- General	783	267	1103	2153
- Regional or field block	25	7	29	61

*Data are means ± SD.

MH⁺ consists of those patients with the following contracture test results: C-MH, CK-MH, H-MH, HC-MH, HCK-MH and HK-MH as defined in Table II.

MH⁻ includes biopsy-negative patients and controls as defined in Table II.

reversible end-organ damage has occurred. Identification of the drugs that trigger MH reactions has also enabled anaesthetists to provide "safe" anaesthesia (i.e., anaesthesia without drugs that trigger MH reactions) for known malignant hyperthermia-susceptible (MHS) patients. This has decreased the incidence of but not eliminated MH reactions in the perioperative period.

Interestingly, several groups have reported a zero incidence of MH reactions after trigger-free anaesthesia in susceptible patients.⁵⁻¹⁰ Although it is tempting to generalize their findings to the entire population of MHS patients, we recommend caution in this regard as these studies lacked sufficient power, i.e., the sample sizes were too small, to estimate the incidence of reactions in the entire population of susceptible patients reliably. In order to determine the incidence of MH reactions in a large cohort of biopsy-positive patients who received a trigger-free anaesthetic, we reviewed the charts of 2,214 patients who underwent elective muscle biopsies for MHS in Toronto between 1971 and 1993.

Methods

The medical records of 2,214 patients who had consented to an elective muscle biopsy were reviewed. In the majority of patients, the indications for muscle biopsy were a previous MH reaction; a family history of an MH reaction, positive muscle biopsy or sign/symptoms of MH; or undiagnosed muscle cramps. In a majority of patients (controls), a muscle biopsy was performed during anaesthesia for an unrelated surgical procedure (usually orthopaedic) that used the same incision. These patients (controls) were without a history of MH susceptibility or myopathy but consented for a muscle biopsy.

All patients were admitted on the night before surgery and a preoperative assessment was completed. An intravenous infusion of lactated Ringer's solution was commenced. The patients were fasted from midnight.

A benzodiazepine (diazepam 0.2 mg · kg⁻¹ or lorazepam 0.03 mg · kg⁻¹) was administered *po* on the evening before surgery and was repeated two hours before

surgery. Morphine 0.1 mg · kg⁻¹ or Pantopon® 0.2 mg · kg⁻¹ was administered *im* one hour before surgery.

On arrival in the operating room, all patients were monitored with an ECG, an automated blood pressure cuff, an axillary temperature probe and a pulse oximeter. End-tidal carbon dioxide tension was monitored routinely after 1987.

A general or regional anaesthetic, or a field-block was used according to the anaesthetist's preference (Table I). For patients who received general anaesthesia, anaesthesia was induced with nitrous oxide and oxygen by mask (delivered via a "vapour-free" anaesthetic machine), Innovar® 1 ml per 15 kg and diazepam or midazolam *iv*. After the trachea was intubated without the aid of muscle relaxants, the lungs were hyperventilated (PaCO₂ 30–35 mmHg) using a Ventimeter® ventilator and either a new Bain or circle circuit with fresh soda lime. Anaesthesia was maintained with nitrous oxide and oxygen and repeated doses of fentanyl *iv* as required.

After induction of anaesthesia, nasal and rectal temperature probes were inserted. All patients were actively cooled using a servo-controlled cooling blanket. The temperature in the operating room was maintained at 17°C. For patients who were scheduled for regional anaesthesia, an epidural or spinal anaesthetic was administered using tetracaine, mepivacaine or lidocaine. For field blocks, lidocaine was used. Muscle was biopsied from the vastus lateralis, rectus femoris or since 1988, the gracilis muscle. The biopsy was immediately mounted between two clamps and immersed in carbogenated Krebs's solution. A small biopsy was also frozen in liquid carbon dioxide and then analyzed as described previously.³

At the completion of surgery, all anaesthetic drugs were discontinued and 100% oxygen was administered. Upon arrival in the recovery room, axillary and nasal temperature sites, heart rate, respiratory rate and blood pressure were monitored for at least four to six hours. If the vital signs were stable, the patient was then transferred to the step-down unit for at least 24 hr.

TABLE II Muscle biopsy results

Category	Diagnosis	In vitro stimulus	Number of patients
MH ⁺	HCK-MH	Halothane alone and caffeine alone and combination*	381
	HC-MH	Halothane alone and caffeine alone	49
	HK-MH	Halothane and combination*	53
	CK-MH	Caffeine and combination*	200
	H-MH	Halothane alone	41
	C-MH	Caffeine alone	84
	K-MH	Combination*	274
		Total	1082
MH ⁻	Non-susceptible	Negative biopsy in a patient who was suspected MHS	936
	controls	Negative biopsy in a patient who was not suspected MHS	196
		Total	1132
		Grand total	2214

*Combination of halothane plus caffeine.

If the vital signs were stable, the patient was then transferred to the step-down unit for at least 24 hr.

Dantrolene was not administered unless an MH reaction was suspected. The halothane/caffeine contracture tests were conducted using criteria that were published previously.¹¹ The laboratory conditions for the *in vitro* contracture response were modified in 1987; the response of 0.25 mM caffeine was replaced by 0.50 mM for the caffeine response test and 1% and 2% halothane were replaced by 3% halothane.

Patients whose contracture test results were positive, were grouped according to their diagnoses: HCK-MH, HC-MH, HK-MH, CK-MH, H-MH, C-MH and K-MH as defined in Table II.

The genealogy of the patients (except control patients) was identified.

Suspected perioperative MH reactions were diagnosed by the attending staff who were unaware of the muscle biopsy results. The diagnosis was based on clinical signs and laboratory data where available. Post hoc, the malignant hyperthermia clinical grading scale (MH rank from 1 to 6)¹² of increasing likelihood that the suspected event was an MH reaction was applied to all presumed MH reactions. The scale depends, in part, on biochemical indices including arterial PCO₂, serum creatine phosphokinase and myoglobin.¹²

Ages were compared using the unpaired Student's *t* test. The incidences of MH reactions (with 95% confidence intervals (95% CI))¹³ among the muscle biopsy groups were compared using Chi-square analysis and Fisher's exact test. Statistical significance was accepted as *P* < 0.05.

Results

The age range of the 2,214 patients in whom muscle

FIGURE The genealogy (as related to the proband) of patients who underwent muscle biopsy for malignant hyperthermia susceptibility according to their contracture test results. Biopsy-positive results (Table II for criteria) are denoted as MH⁺, K-type as K-MH and biopsy negative as MH⁻. Positive muscle biopsies were present in relatives of all orders, even fourth degree relatives and beyond.

was biopsied was 1–95 yr. The mean ages of the biopsy positive and negative patients were similar (Table I). General anaesthesia was administered to 97% of patients and regional anaesthesia or a field block to 3%.

Of the patients who were biopsied, 1,082 were biopsy-positive for MH. The numbers of patients within each subcategory of contracture results are listed in Table II.

The genealogy of 1929 of the patients is summarized in the Figure according to the contracture test results.

TABLE III Suspected MH reactions in patients undergoing muscle biopsy

Demographic data	Case 1	Case 2	Case 3	Case 4	Case 5
Age (yr)	12	24	3	15	26
Sex	Female	Female	Female	Male	Male
Biopsy date (yr)	1977	1977	1979	1981	1984
Contracture test result	K-MH	K-MH	CK-MH	K-MH	HCK-MH
Relation to proband	Daughter	Sister	Proband	Proband	Proband
<i>Characteristics of the MH reaction</i>					
Rigidity	Present	Absent	Absent	Absent	Absent
Hyperthermia	38.8°C	38.1°C*	39.1°C*	39°C*	38.8°C*
Tachycardia (heart rate, bpm)	100/min	120/min	160/min	160/min	100/min
PVC			Occasional		
Hyper-/hypotension	90/50	140†	140†	130†	180†
Tachypnoea (respiratory rate, breaths per minute)		25	40	24	25
Cyanosis			Present		
Drowsiness	Marked				Marked
Arterial blood gas analysis			pH = 7.36, PCO ₂ = 59 mmHg PO ₂ = 64 mmHg HCO ₃ = 22		
CPK (IU/l)	994‡				79

*Rectal temperature.

†Only systolic blood pressure was recorded.

‡25 hr post-biopsy.

The data are based on 798 biopsy-positive (MH⁺) patients, 269 biopsy-positive patients of the K-MH sub-type (K-MH) and 862 biopsy-negative (MH⁻) patients. The genealogy of the remaining patients was not included because either the information was incomplete or the patients were controls.

Five patients (0.46%) developed signs that were suggestive of MH reactions. All five reactions occurred in the recovery room after general anaesthesia. These five patients were subsequently proved to be biopsy-positive for MH; HCK-MH ($n = 1$), C-MH ($n = 1$) and K-MH ($n = 3$). Four of the five patients had had general anaesthesia before: two had developed hyperthermic reactions, another had developed muscle rigidity after succinylcholine without a concomitant increase in temperature and the fourth had three previous uneventful anaesthetics, but had a family history of MH reactions and a positive muscle biopsy in a relative. Four of the five patients were treated with dantrolene *iv*, two of these also received propranolol, chlorpromazine and procainamide. The fifth was treated with vigorous cooling and procainamide since dantrolene *iv* was not available for clinical use at that time. All five patients shivered before the onset of their reactions. Details of the MH reactions are presented in Table III. All five patients survived without additional complications. When the five suspected reactions were ranked using the malignant hyperthermia

clinical grading scale,¹² they scored values of ≤ 4 . This implies that the events were a "somewhat more than likely" MH event.

The incidence of MH reactions in the biopsy-positive patients 5/1082 (0.46%) was similar to the zero incidence in the 1,132 biopsy-negative patients ($P < 0.065$). However, the incidence of reactions in patients with a K-MH contracture result, 3/274, was greater than the incidence in the biopsy-negative patients ($P < 0.007$).

Discussion

In this retrospective review, only five of 1082 patients or 0.46% (0.15–1.07%, 95% CI) who were biopsy-positive for MH, developed clinical signs of acute MH reactions after trigger-free anaesthesia for a muscle biopsy. In contrast to our results, there are several reports of a zero incidence of MH reactions in susceptible patients.^{5–10} Because the sample sizes in those studies were small, we pooled the patient numbers giving a total of 178 biopsy-positive patients (194 including patients with equivocal biopsy results). If we assume that our incidence of reactions (0.46%) is the true incidence, then the probability that 178 susceptible patients will experience no reactions is 44% (41% if the patients with equivocal biopsy results are included).¹⁴ The probability is even greater if the actual sample sizes for the individual studies, rather than pooled sample, are used. Thus, it is not surprising that

no reactions were observed in the smaller published studies.

The upper 95% confidence limit that is compatible with a zero incidence of MH reactions in 178 (or 194 including patients with equivocal biopsy results) is 1.7% (1.6% including patients with equivocal biopsy results).¹⁴ These incidences are more than 50% greater than the upper 95% CI of MH reactions in this study. This difference in the upper confidence interval can be explained by the six-fold difference in the sample size between our study and the pooled studies.

The MH reactions reported in this study are evidence that MH reactions can occur in susceptible patients even after trigger-free anaesthesia.¹⁵ When all of the precautions for MHS are combined (identification of MH susceptibility, use of "clean" or "volatile agent-free" anaesthetic equipment and the avoidance of triggers), the incidence of MH reactions in the perioperative period is small but not zero. Appropriate monitoring, dantrolene and the suspicion that an acute MH reaction may occur at any time, must always be considered in these subjects.

If the standard measures mentioned above cannot prevent MH reactions, then it might seem reasonable to recommend prophylactic dantrolene for all susceptible patients. However, we do not support this strategy for the following reasons. First, the routine use of prophylactic medications is unjustifiable when 99.5% of the affected population will not have direct need of it. Second, side effects and complications from dantrolene *iv* are potentially serious. Dantrolene may increase morbidity when it is administered to a very large population of patients. Third, the effectiveness of prophylactic dantrolene in preventing MH reactions has yet to be established. Fourth, previous studies have demonstrated that acute MH reactions can be managed effectively with dantrolene *iv* provided the diagnosis is made in a timely manner. Fifth, the cost-benefit ratio of prophylactic dantrolene is unproven and would most likely be substantial. On the basis of these arguments, routine prophylactic dantrolene cannot be justified. One exception, however, would be those centres in which the incidence of MH reactions is greater than that reported here. In such cases, prophylactic dantrolene might be justified.

Although the five reactions that occurred in the recovery room were diagnosed as MH reactions, other diagnoses were possible. Shivering may cause tachycardia (present in three of the five patients) and a small increase in blood pressure (present in four of the five patients). All five patients shivered before their reactions were diagnosed and this might have obscured the signs of an MH reaction. Hypoventilation may explain in part, the increase in the PCO₂ observed in at least one patient.

The CPK blood levels when measured were normal. It is possible, but unlikely in our opinion, that these events were not MH reactions.

When we applied the clinical grading scale for MH¹² to score the events in this study, the MH ranks were consistently ≤ 4 or, suggesting a "somewhat greater than likely" chance that these were MH reactions. Although we may have expected a greater rank and therefore a greater likelihood that these were indeed during MH reactions, the maximum scores were limited, in part, by the retrospective nature of this study and the limited data available. The malignant hyperthermia clinical grading scale attributes its score to both clinical and biochemical indices; but, in the present study few biochemical data were available. Consequently, the clinical grading scale and therefore the MH rank of these reactions were based on incomplete data and most likely underestimated the true score. On the basis of the available data and the scores obtained, it is impossible to conclude whether these "events" were indeed MH reactions.

Before 1987, the halothane/cafeine contracture test included the responses to 1 and 2% halothane whereas after 1987,¹⁶ it included only the responses to 3% halothane. This increased concentration of halothane would be expected to decrease the number of false-negative biopsies. However, to date, none of the patients who was biopsied before 1987, has returned for a repeat muscle biopsy to ascertain whether his/her biopsy category has changed. We presume that some of the patients who were biopsied before 1987 and who were biopsy-negative may actually be MH susceptible. However, this presumption remains speculative.

In the present study, all five suspected MH reactions occurred in the recovery room after trigger-free anaesthesia. This is consistent with one published report of three similar cases.¹⁵ Reactions that occur in the recovery room are thought to be less severe than those that occur during general anaesthesia.^{11,17} Nonetheless, they usually present with findings that are typical of an MH reaction including tachycardia, multifocal ventricular arrhythmias, an increase in axillary temperature, and blood/gas abnormalities including hypercapnia, a base deficit and a lowered oxygen tension. Two additional signs have been reported during MH reactions in the recovery room; excessive drowsiness and agitation. All four reactions that were treated with dantrolene in the recovery room in this study terminated rapidly and completely.¹⁷

Although the cluster of presumed MH reactions that occurred in the recovery room might be considered exceptional, there are several substantive reasons to expect MH reactions to occur there. First, the stress of arousal and pain, or shivering may trigger an MH reaction. All five patients who experienced these reactions shivered be-

fore the reactions began. Although none of the five patients was hypothermic on arrival in the recovery room (ambient temperature of 19.5°C), it is possible that they shivered because they had been actively cooled in the operating theatre. Second, trace concentrations of potent volatile anaesthetics in the recovery room may trigger a reaction. Third, the protective effects of certain anaesthetic drugs such as thiopentone, would have dissipated by the time the patient arrived in the recovery room.¹⁸ Individually or combined, these three reasons provide insight into the genesis of MH reactions in the recovery room.

Concerns about the importance of shivering in the genesis of MH reactions has led us to modify our strategy for managing the temperature of susceptible patients in the operating room. Rather than actively cooling them, we have begun to actively warm susceptible patients in the operating room. Several modalities have been used including a warming blanket, a heated humidifier, and increasing the ambient temperature. Although MH reactions have not occurred after a muscle biopsy in susceptible patients since this change was implemented, a cause and effect relationship has not been established. Further studies are required to identify the causal triggers that are responsible for MH reactions in the recovery room.

We conclude that MH reactions can occur after trigger-free anaesthesia for muscle biopsy in susceptible patients. If all five events that occurred in the recovery room were MH reactions, then the incidence of MH reactions after trigger-free anaesthesia in biopsy-positive patients is small, 0.46% (0.15–1.07%, 95% CI).

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